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ADHD subjects fail to suppress eye blinks and microsaccades while anticipating visual stimuli but recover with medication

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ABSTRACT

Oculomotor behavior and parameters are known to be affected by the allocation of attention and could potentially be used to investigate attention disorders. We explored the oculomotor markers of Attention-deficit/hyperactivity disorder (ADHD) that are involuntary and quantitative and that could be used to reveal the core-affected mechanisms, as well as be used for differential diagnosis. We recorded eye movements in a group of 22 ADHD-diagnosed patients with and without medication (methylphenidate) and in 22 control observers while performing the test of variables of attention (t.o.v.a.). We found that the average microsaccade and blink rates were higher in the ADHD group, especially in the time interval around stimulus onset. These rates increased monotonically over session time for both groups, but with significantly faster increments in the unmedicated ADHD group. With medication, the level and time course of the microsaccade rate were fully normalized to the control level, regardless of the time interval within trials. In contrast, the pupil diameter decreased over time within sessions and significantly increased above the control level with medication. We interpreted the suppression of microsaccades and eye blinks around the stimulus onset as reflecting a temporal anticipation mechanism for the transient allocation of attention, and their overall rates as inversely reflecting the level of arousal. We suggest that ADHD subjects fail to maintain sufficient levels of arousal during a simple and prolonged task, which limits their ability to dynamically allocate attention while anticipating visual stimuli. This impairment normalizes with medication and its oculomotor quantification could potentially be used for differential diagnosis.

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1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a common behavioral disorder with a genetic component (Guan et al., 2009). *The Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5)* (American Psychiatric Association, 2013) describes attention-deficit/hyperactivity disorder as characterized by inattention, impulsivity, and/or hyperactivity. These three subtypes were found to be similar regarding the mean age, gender ratio, prevalence, and pattern of associated learning disabilities, the family history of psychopathology, and the probability of a favorable response to methylphenidate (de Quiros et al., 1994). ADHD affects 3–10% of children in the United States, one to two thirds of whom will continue to suffer from this disorder throughout adulthood (Wender, Wolf, & Wasserstein, 2001). A recent review concluded that "The substantial societal burden of adult ADHD highlights the importance of providing a better understanding of the factors that contribute to accurate diagnosis and of improving the low recognition of the disorder in many world regions" (Asherson et al., 2012). Several computerized continuous performance tests (CPT) aim to provide better diagnostics; the most used CPT is the "test of variables of attention" (t.o.v.a.) (Greenberg & Waldman, 1993). However, the reliability of t.o.v.a. as a screening diagnostic tool is still debated (Zelnik et al., 2012).

Currently, the most effective treatment for ADHD is to use medications containing the chemical compound methylphenidate (MPH) (Arnsten, 2006). In general, psychostimulants such as MPH have been found to be the most effective drugs for reducing

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symptoms of inattention, hyperactivity, and impulsivity in patients with ADHD, and they can enhance specific aspects of cognitive performance (Agay et al., 2010).

In recent years there has been an attempt to find a reliable diagnostic tool based on physiological markers. One of the areas of investigation is the visual system (Martin et al., 2008; Poltavski, Biberdorf, & Petros, 2012), with a potential interest in the pattern of microsaccades, as well as pupil dilation.

Microsaccades, which are small saccades associated with visual fixation, have been recently linked with attention, both in space (biasing microsaccade direction) (Laubrock et al., 2010; Pastukhov & Braun, 2010) and time (Pastukhov et al., 2012). In response to perceptual events, microsaccades are typically inhibited for a duration that depends on the stimulus parameters and attention (Rolfs, 2009). Anticipated events are preceded by microsaccade inhibition (Betta & Turatto, 2006), and reaction times are typically faster when microsaccades are inhibited around stimulus onset (Kliegl et al., 2009). Moreover, higher attentional load is associated with lower microsaccade rates (Pastukhov & Braun, 2010), and attended as well as surprising stimuli induce prolonged inhibition (Bonneh et al., 2011, 2012; Valsecchi, Betta, & Turatto, 2007). Although microsaccades have not been analyzed in ADHD patients so far, one study found that these patients have significantly more saccades (>2°) during prolonged fixation in an antisaccade task (Munoz et al., 2003). The link between microsaccades and the allocation of attention was recently summarized in a review (Martinez-Conde, Otero-Millan, & Macknik, 2013). In sum, the pattern of microsaccadic response to perceptual stimuli as well as the ongoing modulation of the microsaccade rate under attentional demands could potentially be used to characterize the variables of attention.

Blink rate has also been linked with mental states and attention, suggesting a possible diagnostic value in ADHD patients. For example, blink rates were found to be negatively correlated with arousal (Tanaka, 1999) and increase with prolonged wakefulness (Barbato et al., 2007), presumably due to a reduction in inhibitory control. In line with these findings, a study of patients with chronic schizophrenia found that the blink rates in free viewing were correlated with signs of disinhibition (Chan & Chen, 2004).

Pupil diameter is another ocular parameter that has been known for many years to correlate with mental activities (Kahneman & Beatty, 1966), and it could also be used to measure the level of arousal (Bradshaw, 1967). Apart from its main function, which is to control the amount of light entering the eye, the pupil diameter was also found to respond to a number of other factors. The pupil dilates in response to increased activity of the sympathetic system and constricts in response to increased parasympathetic activity. Thus, any change in the balance between the two systems will affect the pupil diameter. Drugs that change this balance, such as MPH, will also affect the diameter of the pupil (Nagyova et al., 2007). Past studies showed that the pupil diameter changes under various cognitive tasks (Kahneman & Wright, 1971; Simpson, 1968). Similar to the microsaccade rate, although with a different dynamics, the pupil diameter typically shows a transient increase in response to perceptual events, with a magnitude and time course that depends on various stimulus parameters such as repetition and surprise (Privitera et al., 2010). Moreover, a recent study found that “intentional changes in attentional spread” correlated with changes in pupil diameter (Daniels et al., 2012).

Taken together, these studies show that different ocular parameters correlate with cognitive and attentional functions. The aim of the current study was to investigate a possible difference in these parameters between ADHD-diagnosed and control subjects in a task that involves dynamic allocation of attention as opposed to passive fixation in which no difference was found between ADHD-diagnosed and controlled subjects (Gould et al., 2001). Our additional aim was to investigate the effect of medication on these parameters, and specifically whether it normalizes them as it normalizes behavior.

2. Methods

2.1. Participants

The participants consisted of 22 adult volunteers, mean age 33.9 ± 13.1, 12 males and 10 females, previously diagnosed with ADHD, using DSM-IV-TR criteria (American Psychiatric Association, 2000), and 22 control subjects, mean age 31.4 ± 8.5, 10 males, and 12 females. All the participants were tested in our laboratory for visual acuity and were found to have normal or corrected-to-normal vision. Except for one subject diagnosed with additional Dysthymia and Social Anxiety, no other comorbidity was diagnosed in the ADHD group. Each subject signed an informed consent form approved by the local Institutional Review Board of Sheba Medical Center.

2.2. Medication

ADHD-diagnosed subjects had all previously been prescribed medication containing methylphenidate, and all of them had taken the medication before and reported that it increased their performance in various daily activities. In our study, the subjects were asked to take one dose of their individually prescribed medication, which consisted of different formulations of methylphenidate – Immediate release (IR Ritalin), OROS methylphenidate (Concerta), and long-acting (Ritalin LA), and after 1.5 h of administration, all formulations were found to have similar bioavailability (McBurnett & Starr, 2011).

2.3. Stimuli and procedure

A session consisted of a sequence of 648 trials, each consisting of the commonly used t.o.v.a. stimuli presented for 100 ms every 2 s. A “target” and a “non-target” (see Fig. 1) consisted of a white square of 9.5 × 9.5 cm (9° × 9° of visual angle) with an inner black square of 1.2 × 1.2 cm (1.15° × 1.15°), positioned 0.7 cm from the top (for target) or bottom (for non-target) of the bright white square. The luminance of the background, as well as of the small inner square, was 0.2 CD/m^2 and the luminance of the bright square was 58 CD/m^2. A small fixation dot, ∼0.03° in diameter, was constantly presented at the center of the display, with the same luminance as the bright square. The stimuli were presented in random order for about 22 min. In the first half of the session (the “rare” part) the target stimulus appeared randomly only for

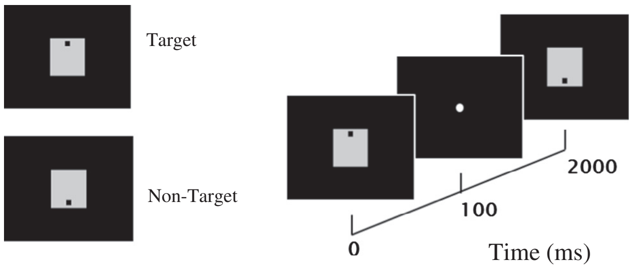

Fig. 1. Stimuli. A “target” (left top) or “non-target” (left bottom) was presented for 100 ms every 2 s in random order, as demonstrated schematically on the right. The size of the white square was 9.5 × 9.5 cm and the size of the inner black square was 1.2 × 1.2 cm, 0.7 cm from the edge of the white square. The viewing distance was 60 cm. Q4

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22% of the trials, whereas in the second half of the session (the "frequent" part) the target rate was 78%.

The stimuli were presented using an in-house-developed platform for psychophysical experiments (PSY) developed by the third author (YB) and were integrated with an eye tracking system. The target stimuli were shown on a Brilliance 109P CRT display monitor. The refresh rate was set to 100 Hz and the pixel resolution was 1024 × 768. The viewing distance was 60 cm in a darkened room.

Each subject performed the session twice in one day. ADHD-diagnosed subjects performed the first session before taking the medication (which will be referred to as "ADHD"), and performed the session again 1.5 h after taking the medication ("ADHD-M"). Control subjects also performed the session twice with a 1.5 h break in between the sessions (which will be referred to as "Control-1" and "Control-2", respectively). We have chosen this same-day design to avoid across-days variability and also owing to the difficulty in recruiting subjects for multiple days of testing, which would have reduced our sample. Since there is a long washout period for MPH, we used a fixed order medication-last design, and in order to control for possible carry-over effects attributed to either learning or fatigue, the control subjects also ran the session twice, with the same time gap between sessions. Note that in a study that checked test–retest reliability, employing the same inter-test gap of 1.5 h as we did, no significant change was found in reaction time (Leark, Wallace, & Fitzgerald, 2004).

The task was to respond as fast as possible to targets and to ignore non-targets. The subjects were instructed to press the left mouse button as fast as they can, without mistakes as much as possible, following the presentation of a target stimulus, and to ignore non-target stimuli. Another instruction, which is not part of the standard t.o.v.a., was to maintain fixation on the fixation dot at the center of the screen.

2.4. Tracking eye movements

We recorded eye movements during the sessions with an EyeLink® 1000 desktop model from SR-Research. The subjects' head was stabilized with a chin-rest. We tracked only the dominant eye. Before each session we calibrated the system in order to obtain an accurate gaze position. Eye tracking data were sampled at 500 Hz and stored for offline analysis.

2.5. Data analysis

2.5.1. Blinks, microsaccades, and pupil diameter

Blinks were detected as periods of no tracking data. Microsaccades were detected by an algorithm developed by the first author, which was successfully used in another study (Bonneh et al., 2010). Prior to microsaccade detection, the data were smoothed by a low-pass filter with a cut-off frequency of 120 Hz. The algorithm then detected sequences of data samples representing eye movement for at least 6 ms in the same direction (with a 30° window), with the minimum velocity, checked with each sample, exceeding 10°/s, a peak velocity exceeding 18°/s, and a saccade amplitude greater than 0.1°. Saccades with amplitudes >2° were ignored for the main analysis. Dynamic overshoots, which are smaller amplitude microsaccades that immediately follow a microsaccade in the opposite direction, were counted together with the main microsaccade. Sections of blinks were excluded from saccade detection and were considered as durations with no microsaccades. Furthermore, to prevent false detection of microsaccades around blinks, we excluded an additional 20 ms before and after each blink. Pupil diameter data were taken at stimulus onset and converted into millimeters using a conversion factor obtained by recording an artificial eye, with a fixed pupil diameter, in the same experimental setup. All the trials in all the sessions were included in the analysis.

2.5.2. Group averages and statistics

Group averages were computed and analyzed as follows. We calculated, for each session, the average blink and microsaccade rates for the entire trial duration and also during the peri-stimulus interval only (−100 to 150 ms relative to stimulus onset). Data for target and non-target trials as well as for the "rare" and "frequent" halves of each session were pooled together for calculating group averages because they showed no significant difference in the peri-stimulus interval. We then computed group averages for: (1) ADHD, (2) ADHD-M, (3) Control-1, and (4) Control-2.

For statistical analysis of the group averages of microsaccade and blink rates, the results were first entered into ANOVA (2 groups × 2 tests); pairwise comparisons were performed using two-sample and paired *t*-tests, as specified. The degree of freedom was 42 ($2n-2$) for the 2-sample *t*-test and 21 ($n-1$) for the paired *t*-test.

2.5.3. Rate modulation in a trial

Microsaccade and blink rate modulation functions throughout the trials, time-locked to stimulus onset, were computed as follows. In each trial, blinks (or microsaccades) were summed as Gaussians with the center at the time of onset and with a sigma of 20 ms to obtain a rate modulation function per trial. These rate modulations were averaged per session and per subject, and then averaged per group. Error bars were computed to reflect one standard error of the group mean at each data point. A similar method was used successfully in a previous study (Bonneh et al., 2010) and is used here for both microsaccades and blinks (see Fig. 10).

2.5.4. Time-course in a session

The time courses of microsaccade and blink rates as well as pupil diameter across the 22 min sessions were computed as follows. Using a time bin of a single trial, respective rates were computed for each trial in a session, averaged per observer and then averaged by group to obtain standard error values. This procedure was done twice: once for the peri-stimulus interval only and again for the entire trial duration excluding the peri-stimulus time interval (see Fig. 11).

3. Results

The results are reported below; they are divided into separate sections for each of the 3 ocular parameters investigated: blink rate, microsaccade rate, and pupil diameter. Group averages were computed across all the trial durations (2 s) or only during the peri-stimulus time interval within each trial. Additional sections summarize the time course of these parameters within a trial and across the session as well as the effect of medication. We found that the unmedicated ADHD group differed from the control group, showing reduced suppression of microsaccades and blinks when they had to be suppressed, and a recovery from these abnormalities with medication.

3.1. Blink rate

Fig. 2 shows a raster plot of eye blinks during a t.o.v.a. session of a sample unmedicated ADHD-diagnosed subject (a) and of a sample control subject (b). As can be clearly seen, there are no blinks in the interval prior to, during, and shortly after stimulus presentation in the control subject, whereas there are many blinks in this interval in the unmedicated ADHD subject. Fig. 3 shows the average blink rate of the four test groups throughout the session (a) and only during the peri-stimulus interval (b). There was a significantly higher average blink rate in the ADHD group compared with the control group, in both the first and the second tests

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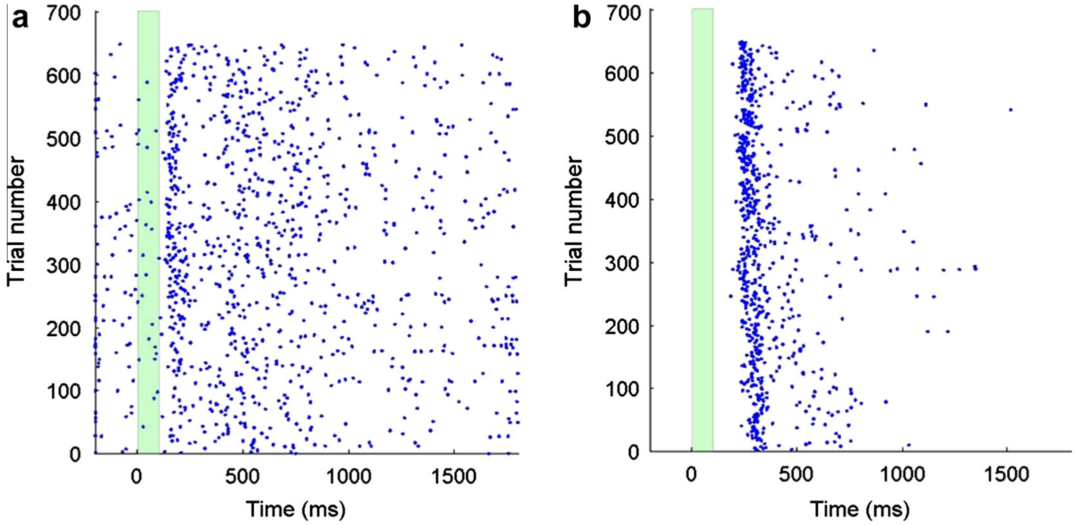

Fig. 2. Eye blinks. Raster plot of eye blinks during a t.o.v.a. session of a sample unmedicated ADHD-diagnosed subject (a) and of a sample control subject (b). Each blue dot represents the onset time of a single eye blink. The green bar represents the time interval of stimulus presentation. As shown, there are no blinks in the interval prior to, during, and shortly after stimulus presentation in the control subject, whereas in the unmedicated ADHD subject there are many blinks during this interval. Furthermore, in the control subject the blinks are highly synchronized with the stimulus presentation, whereas in the ADHD subjects the blinks are much less synchronized. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

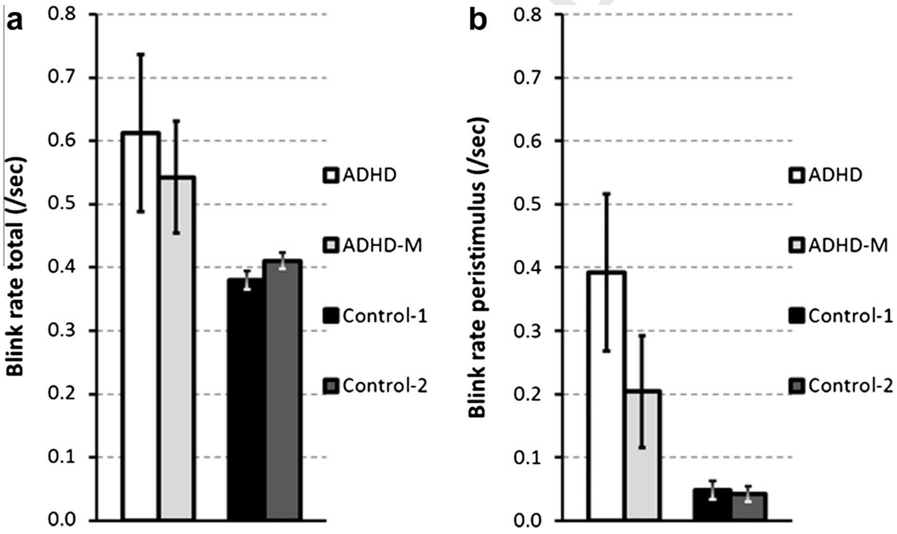

Fig. 3. Blink rates. Group averages of blink rates throughout the t.o.v.a. sessions (a) and for the peri-stimulus interval (b). The average blink rates of unmedicated ADHD subjects throughout the session are significantly higher than those of the control subjects and they are reduced towards a normal range for subjects with medication. The blink rates of unmedicated ADHD subjects, checked only during the peri-stimulus interval, are significantly higher than the rates of control subjects. This higher rate is significantly reduced to about half the rate of subjects with medication, but it still remains significantly above the control rate.

(ANOVA (2 groups × 2 tests), group effect: $F(1,84) = 5.5$, $p = 0.022$), test effect: n.s, interaction: n.s.). As can be seen, the average blink rate in the unmedicated ADHD group is significantly higher than in Control-1 ($p = 0.033$, two-sample t-test), with no significant change between Control-1 and Control-2 ($p = 0.398$) or medicated ADHD and Control-2 ($p = 0.255$, two-sample t-test). In comparison, as shown in Fig. 3 (b), unmedicated ADHD subjects failed to synchronize their blinks to avoid blinking during an anticipated stimulus presentation group effect: $F(1,84) = 11.4$, $p = 0.001$, test effect: n.s., interaction: n.s. However, this capacity is significantly improved with medication ($p = 0.034$, paired t-test), and it still remains above the control rate ($p = 0.007$) in the first test and approaches significance ($p = 0.069$) in the second test, the two-sample t-test.

Note that the average blink rates of all test groups were around 30 blinks/min, higher than a rate of 23/min, previously reported for normal adults (Karson, 1983). This could be due to the subjects' tendency to synchronize their blinks with the task in order to avoid blinking during the anticipated stimulus presentation, as indicated by the synchronized blink rate modulation (Figs. 2b and 10a), and in line with the stimulus rate (30/min). This difference could also be explained by the change in blink rate throughout the session (Fig. 11e), starting at rates only slightly above 20 blinks/min for the controls.

3.2. Microsaccade rate

Fig. 4 shows the microsaccades peak velocity–magnitude relationship, also known as the "main sequence", in a representative ADHD and a control subject during the entire session. The data show a similar main sequence and the amplitude range for the two subjects; however, there were more microsaccades for the

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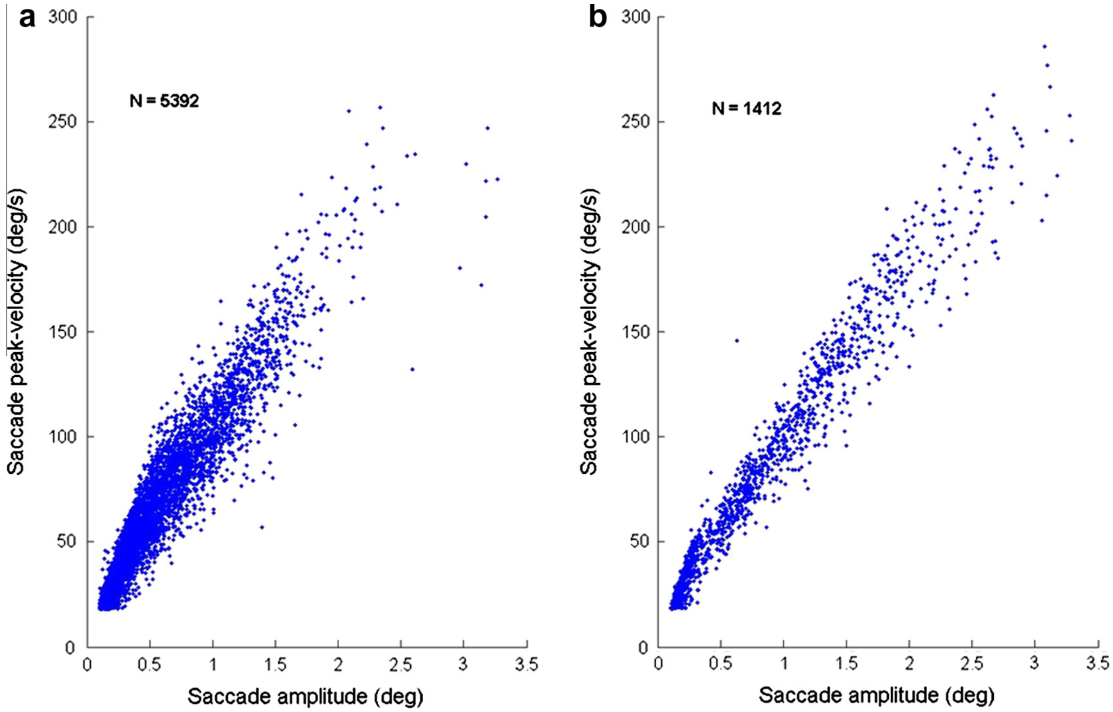

Fig. 4. Saccade main sequence. The microsaccadic peak velocity–magnitude relationship in a representative (a) ADHD and (b) control subject, during one full session. Note that both subjects exhibit a similar main sequence and amplitude range, although the ADHD subject has more microsaccades (N label in the plot).

ADHD subjects, consistent with the group average data described below. These data are consistent with the standard main sequence effect in the literature, e.g. (McCamy et al., 2012).

Fig. 5 shows a raster plot of microsaccades during a t.o.v.a. session of a sample unmedicated ADHD subject (a) and of a sample control subject (b). As shown, few microsaccades were detected in the interval prior to, during, and shortly after stimulus presentation in the control subject, whereas there were many microsaccades in this interval in the unmedicated ADHD subject.

Fig. 6 shows the average rates of microsaccades for the four test groups throughout the session (a) and only during the peri-stimulus interval (b). As shown, when microsaccade rates are averaged only during the peri-stimulus interval, the rates in the unmedicated ADHD group are significantly higher than those in controls (group effect: $F(1,84) = 6.4$, $p = 0.014$, test effect: $F(1,84) = 6.5$, $p = 0.013$, interaction: $F(1,84) = 5.2$, $p = 0.025$). Moreover, the rates are reduced in the medicated ADHD group ($p = 0.001$, paired t-test) compared with the control group rates (p = n.s., two-sample t-test). In addition, the average rate of microsaccades throughout the t.o.v.a. session, in the unmedicated ADHD group, is significantly higher than in the control group (group effect: n.s., test effect: $F(1,84) = 7.9$, $p = 0.01$, interaction: n.s.; $p = 0.06$, two-sample t-test). This higher average rate is reduced to the average control rate with medication ($p < 0.001$, paired t-test).

We further investigated the microsaccade rate differences across groups, by examining their amplitude distributions.

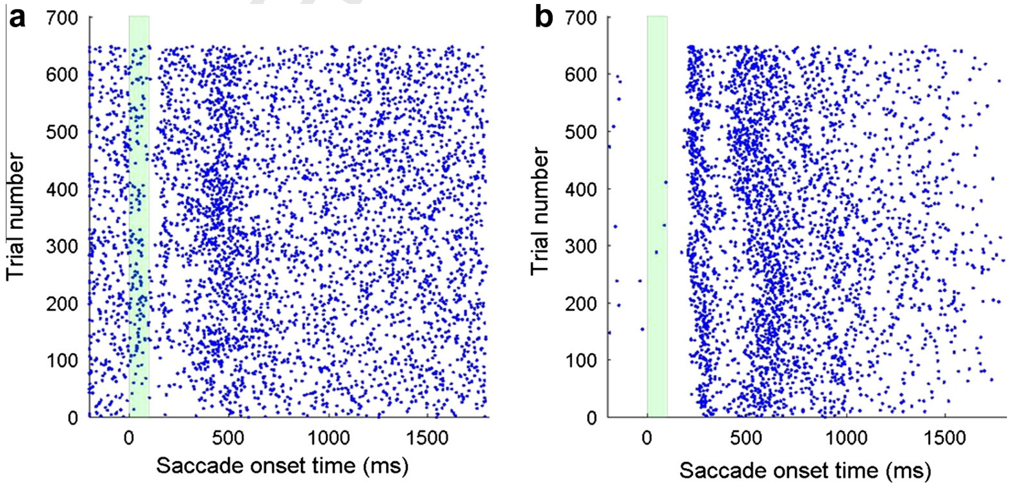

Fig. 5. Microsaccades. Raster plot of microsaccades during a t.o.v.a. session of a sample unmedicated ADHD-diagnosed subject (a) and of a sample control subject (b). Each blue dot represents the onset time of a single microsaccade. The green bar represents the time interval of stimulus presentation. As shown, there are few microsaccades, in the interval prior to, during, and shortly after stimulus presentation in the control subject, whereas in the unmedicated ADHD subject there are many microsaccades in this interval. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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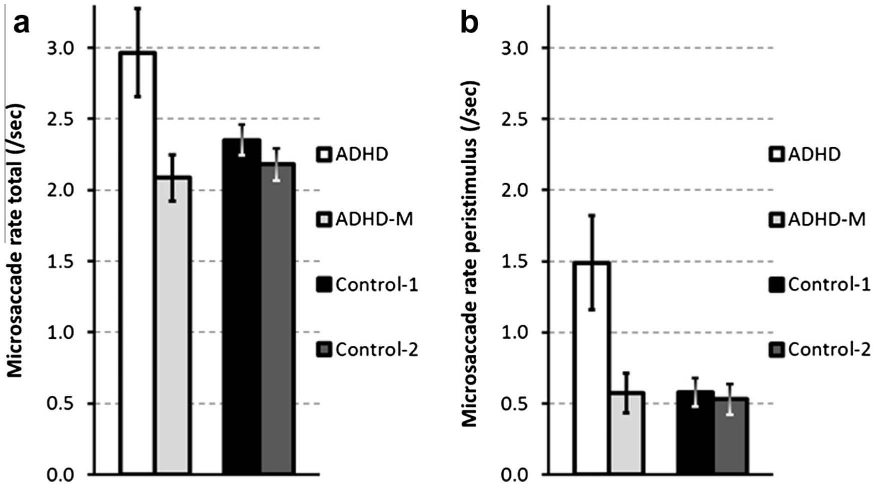

Fig. 6. Microsaccade rates. Average microsaccade rates for each of the four test groups. Throughout the t.o.v.a. sessions (a) the average rate of microsaccades in the unmedicated ADHD group was significantly higher than that of the control groups, and it was reduced to the normal range in the medicated group. The average microsaccade rate in the unmedicated group during the peri-stimulus interval (b) was significantly higher, almost threefold, than the rate of the control subjects. This higher rate was reduced to the level of the control rates in the medicated group.

The results are plotted in Fig. 7. As shown, there is a higher rate of microsaccades in the ADHD group in all the amplitude ranges, but this difference is highest around 0.2°.

3.3. Manual reaction time

In order to verify that our microsaccade and blink rate measurements are correlated with standard t.o.v.a. behavioral measurements, we computed the average standard deviation of the manual reaction time (RT-STD) for the four groups (which is the main component of the t.o.v.a. score). Fig. 8 shows that both average RT and the average RT-STD was significantly higher in the unmedicated ADHD group compared with controls ($p = 0.04$ and <0.001, RT and RT-STD, respectively, two-sample t-test), and that it was reduced to the control level with medication (p = n.s. for both RT and RT-STD, two-sample t-test).

We further investigated the correlation between the ocular parameters (microsaccade and blink rates) and the manual response time variability (RT-STD). The results are summarized in Table 1, showing a significant correlation for the microsaccade rate in the peri-stimulus interval (MS-peri) for all groups, and especially for the ADHD groups ($R > 0.5$); however, there was a lower but still significant correlation for the blink rate only for the ADHD groups (R around 0.3).

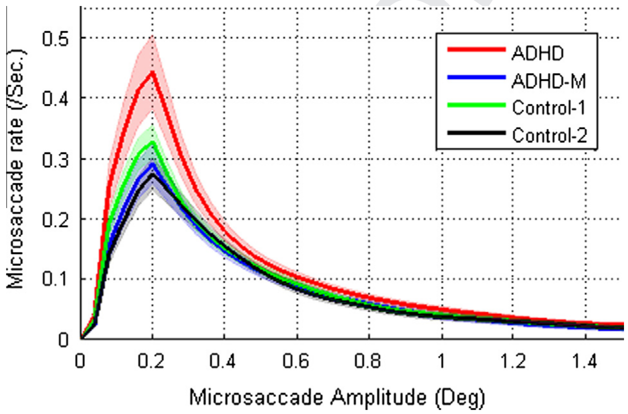

Fig. 7. Microsaccade amplitude distribution throughout the whole trial for each of the four groups. Data were averaged per observer across all saccades within a trial, divided into amplitude bins, and then averaged across all observers in the group. Error sleeves denote 1SE across observers. Note that the main difference in the unmedicated ADHD group lies in the small and frequent microsaccades around 0.2°.

3.4. Pupil diameter

Fig. 9 shows the average pupil diameter and the average variability at the time of stimulus onset for the four conditions (group and experiment). No significant difference regarding the average pupil diameter (Fig. 6a) was found between conditions (group effect: n.s., test effect: n.s., interaction: n.s.), except for a small effect of larger pupil diameter with medication ($p = 0.041$, paired t-test). Pupil diameter variability (STD) did not differ significantly between groups in the first test, or between the first and second test for the controls (Fig. 6b), but it was significantly reduced with medication (group effect: $F(1,84) = 5.5$, $p = 0.022$, test effect: n.s., interaction: $F(1,84) = 4.1$, $p = 0.047$), both compared with the test before medication ($p < 0.001$, paired t-test) and with the second test of the control group ($p = 0.03$, two-sample t-test). Additional results related to the time course of pupil diameter modulation throughout the session are described next.

3.5. Modulation of ocular parameters across time

We analyzed the time course of microsaccade and blink rates within the 2 s trials, as well as the time course of all the ocular parameters across the 22 min sessions.

3.5.1. Rate modulation within a trial

Fig. 10 shows the time course of the microsaccade and blink rates within a trial. These functions were calculated per trial and averaged across all target and non-target trials of both rare and frequent session halves per observer, then averaged across all observers in each group (see Section 2). The general pattern of these time courses, as shown for the controls, is a rate reduction that starts before the anticipated stimulus onset and reaches almost a zero rate about 100 ms after onset, followed by a release from inhibition around 400–500 ms, and then a slow decrease towards the next anticipated stimulus, which appears every 2 s. The ADHD group deviates from the controls by (1) an elevated rate (both regarding microsaccades and blinks) prior to and immediately after the stimulus, but it failed to reach full suppression at around 100 ms;

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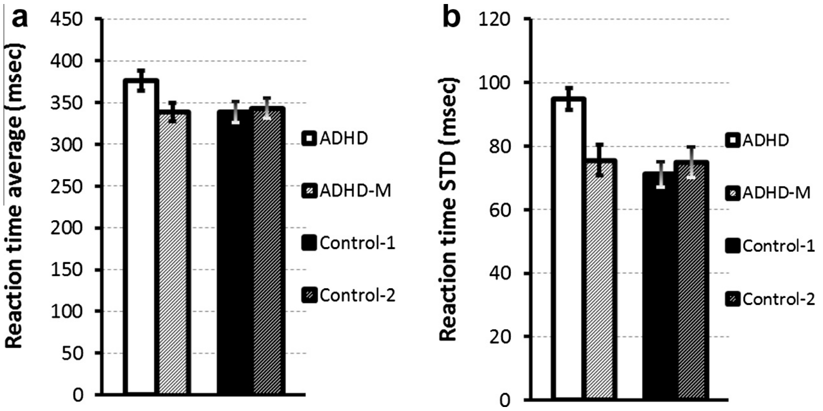

Fig. 8. Manual reaction-times. Average manual reaction times (a) and the average standard deviation of the four groups (b). Both the average and the RT-STD were significantly higher in the unmedicated ADHD group compared with controls and were reduced to control levels with medication.

Table 1
Correlation between manual reaction times standard deviation (RT-STD) and the main ocular parameters of microsaccade and blink rates. The correlation coefficient *R* was computed using individual subject data from each group, separately for the peri-stimulus and the whole trial interval. Note the significant correlation ($R > 0.5$) for the microsaccade rate in the peri-stimulus interval for the ADHD groups and the lower but still significant correlation of the blink rate for these groups.

RT-STD vs.	MS peri	Blink peri	MS total	Blink total
ADHD	0.56	0.35	0.40	0.08
ADHD-M	0.66	0.26	0.60	−0.09
Control-1	0.41	0.08	0.07	−0.09
Control-2	0.39	0.04	0.07	−0.25
Across groups	0.57	0.35	0.42	0.04

(2) higher tonic rates after 1 s, with less anticipatory reduction towards the next stimulus; (3) a delayed peak for the blink rate. The results for the medicated ADHD group for microsaccades appear to be very similar to those of the first experiment using the controls, and are identical regarding the initial suppression at around 100 ms, i.e. the medicated ADHD patients showed normal control over their microsaccades prior to and immediately after the stimulus onset. Medication reduced also the blink rate, but to a lesser extent and only during the period before stimulus onset. These data are provided here for the purpose of qualitative comparison, and for pointing out the most informative time intervals, which we investigated statistically via group averages.

3.5.2. Rate modulation across the session

Fig. 11 shows the time course of the ocular parameters across trials within the 22 min sessions. Group averages are plotted for microsaccade rate, blink rate, and pupil diameter for two time intervals in each trial: the peri-stimulus and post-stimulus (Fig. 11, left and middle columns), as well as the ratio between them (Fig. 11, right column). These plots show the findings of the current study in more detail and point out the striking difference in the ocular behavior of the unmedicated ADHD patients summarized below and the striking normalizing effect of medication, which will be described next.

The results can be summarized as follows: (1) Saccade and blink rates show a similar general trend (Fig. 11, top and middle row). They increase with time in the post-stimulus interval and are lower for the peri-stimulus interval than for the post-stimulus interval. This effect is strongest for the blink rate of the control groups, where rates approach zero in the peri-stimulus interval throughout the session (Fig. 11d). This was demonstrated by the ratio plots (Fig. 11, right column), since the ratio values are all below 1 (around 0.2 for the controls). (2) The unmedicated ADHD group (Fig. 11, in red) shows a much higher tonic level of saccade and blink rates than do the other groups throughout the trial, possibly due to a lower level of arousal, which is necessary for oculomotor inhibition. In addition, an interval-specific effect is

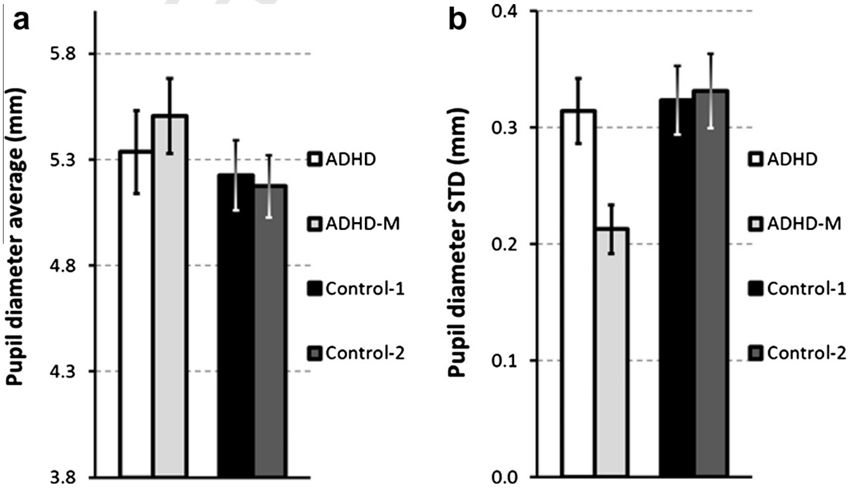

Fig. 9. Pupil diameter. Average pupil diameter of the four groups sampled at stimulus onset (a) and its standard deviation (b). Though statistically insignificant, the average pupil diameter of the medicated ADHD group is higher than that of the control group, and is significantly higher than before medication within the ADHD group, which is a known physiological response to MPH. However, the variability of the pupil diameter in the unmedicated group is about the same as in both control groups, but it is significantly reduced in the ADHD group with medication.

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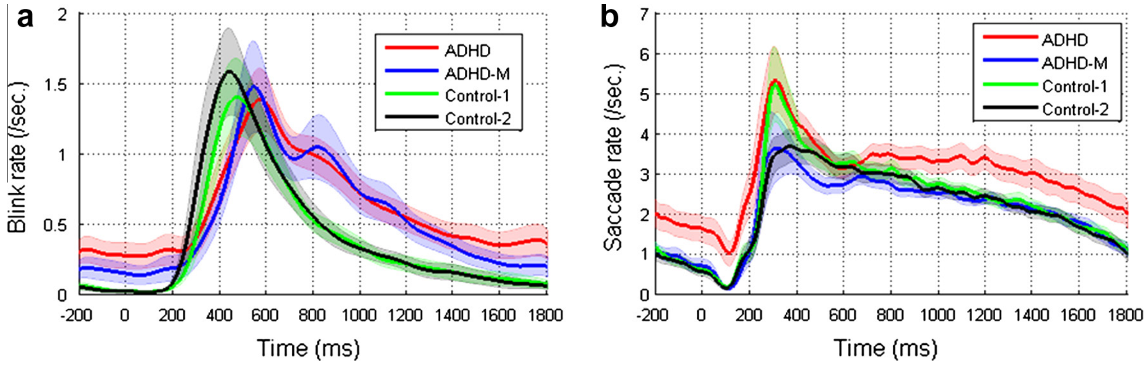

Fig. 10. Average blink (a) and microsaccade (b) rate modulation within trials, time locked to the stimulus onset (0), for each of the four groups. Data were averaged across all trials, including targets and non-targets, for each observer, and then averaged across observers ($N = 22$) for each group, with error bars denoting 1SE of this average. Note the higher microsaccade and blink rates in the ADHD group before and immediately after stimulus onset, and the full normalization effect of medication on microsaccades (b, blue). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

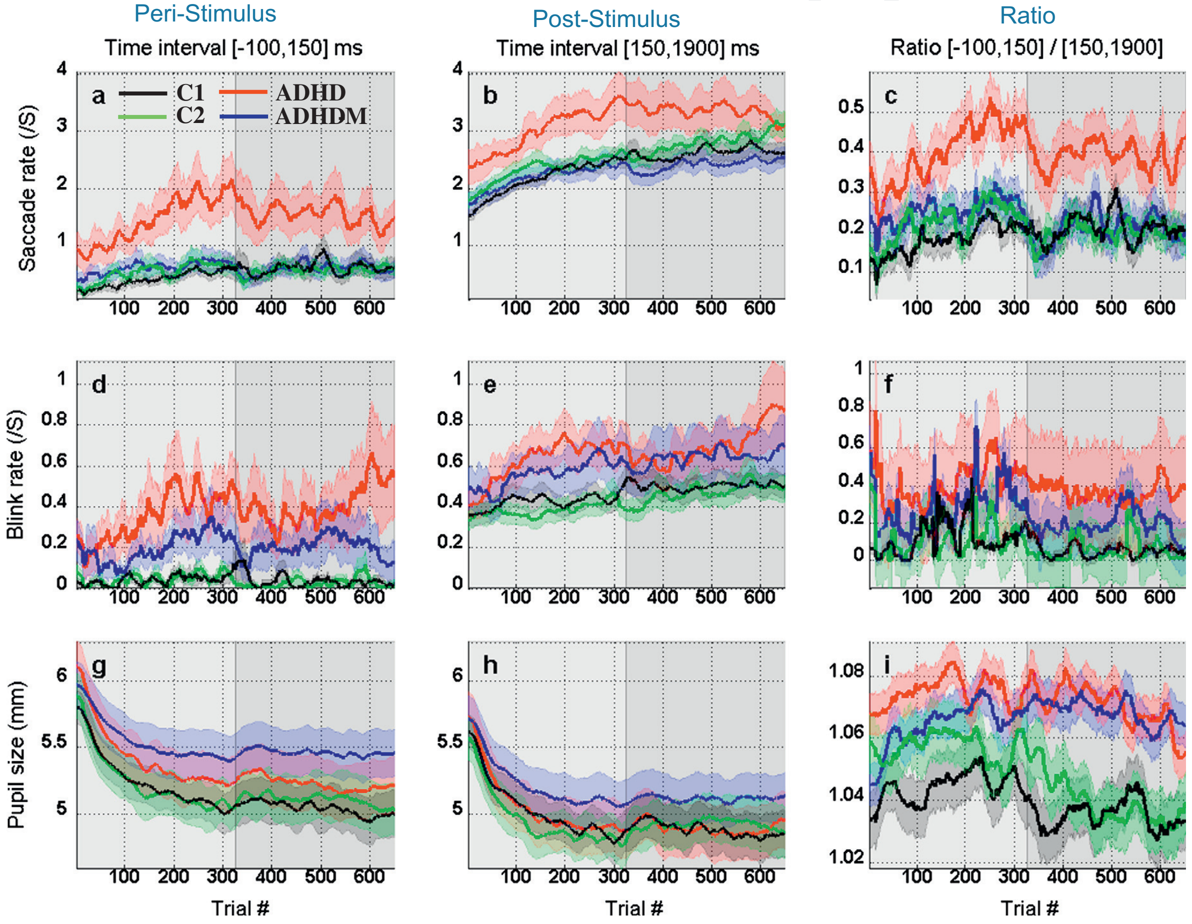

Fig. 11. Ocular parameters' modulation over time within a session. Group averages of 3 ocular parameters (rows) were computed in 2 time intervals within a trial (peri-stimulus [−100, 150], and post-stimulus [150, 1900] relative to stimulus onset), as well as the ratio between them (columns). The parameters shown are the saccade rate (a–c), blink rate (d–f), and pupil size (g–i). The solid lines correspond to the different groups and conditions: ADHD, ADHD-M (with medication), C1 (controls, 1st session), and C2 (controls, 2nd session). Each point in the solid lines represents the group average for a trial in the session, with shaded areas showing ±1 SE of these averages. The *x*-axis shows the trial number (1–648) corresponding to the ~22 min sessions divided into "rare" and "frequent" halves (see Section 2) by different shades of gray. Note that all parameters change with time across the session for all groups, increase (saccade and blink rates), or decrease (pupil size). The unmedicated ADHD group (in red) stands out strikingly, especially for the saccade rate in the peri-stimulus interval, whereas the medicated ADHD group (in green) appears strikingly similar to the control groups for the saccade and blink rates, but not for the pupil size. See the text for more details. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

demonstrated by the ratio plots (right column), showing more than a twofold higher ratio for the unmedicated ADHD group compared with controls, which implies a specific impairment in suppressing saccades and blinks around the stimulus onset. (3) The pupil diameter decreased with time for all groups, possibly reflecting adaptation to the task, which is accompanied by reduced vigilance or arousal (Honda et al., 2013). (4) Following the change in target frequency ("rare" to "frequent") in the middle of the session, there

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was a decrease in the microsaccade and blink rates in both time intervals and an increase in pupil diameter in all groups. These changes reflect the effect of the additional attentional load and effort owing to the change in the task.

3.6. The effect of medication

The results for the medicated ADHD group stand out as a striking effect of normalization, as found for microsaccade and blink rates (Fig. 11, two upper rows, blue curves), and especially for microsaccades. In Fig. 11a, the strong elevated microsaccade rate of the unmedicated ADHD group (in red) is totally normalized to the level of the controls (compare the blue curve to the black and green curves). This could not be a re-test effect, because no such effect was found between the two tests of the control group. A similar normalization effect was found for the post-stimulus interval (Fig. 11b) and hence for the ratio as well.

The medication effect on the blink rate is similar to that of the microsaccades, but the normalization effect is only partial. In the peri-stimulus interval (Fig. 11d), the medicated blink rate curve (in blue) appears half way between the unmedicated group and the controls. A smaller effect with the same trend was found for the post-stimulus interval (Fig. 11e), possibly because the margin for improvement with medication under that condition was small. This is also reflected in the ratio plot (Fig. 11f), which shows a normalization effect with medication despite very large variability.

However, a very different effect of medication was found regarding the pupil diameter (Fig. 11g–i). As shown, the unmedicated group had a slightly larger pupil diameter in the peri-stimulus, but not in the post-stimulus interval. Not only was the pupil size not normalized with medication, it even became larger in both the peri- and post-stimulus intervals (compare the blue to the other curves). This implies that the improvement in the inhibitory power with medication, as demonstrated in the reduced microsaccade and blink rates around stimulus onset, had a cost – it was achieved by elevating the general level of arousal significantly above normal, as reflected in the larger pupil diameter.

We considered the possibility that the presumed effect of medication reflects a practice effect, not found in the control group due to a "floor" effect (microsaccade and blink rates that had already reached very low values in the first session). One argument against this possibility is the evidence for no test/retest effects in the t.o.v.a. paradigm in terms of RT average and variability (Leark, Wallace, & Fitzgerald, 2004), and our finding of a correlation between microsaccade rates and manual RT variability. This implies that the improvement in the medicated ADHD group is unlikely to reflect the effect of practice.

To further investigate the suspected effect of practice, we recalled 5 subjects from the ADHD group and had them run the sessions twice without medication and with a gap of 1.5 h. We found a slight deterioration rather than improvement of the saccade rate (in the peri-stimulus interval) and of the manual RT variability in the second recall run, compared with the first, i.e. no practice effect without medication. In addition, these results showed no significant difference from the first (unmedicated) recording in the main experiment. We therefore can conclude that our measures reflect the true effect of medication, which is not due to practice.

3.7. Using ocular parameters for diagnosis: preliminary results

In order to obtain a preliminary estimate for the classification power of our ocular parameters, we applied a simple linear classification approach to our sample, using the microsaccade and blink rates in the peri-stimulus interval, where the difference between the group averages was the largest. The results are shown in Fig. 12, with rates converted to log units (log10(rate + 0.01)). This preliminary classification yielded an accuracy of 70%, a sensitivity of 59%, a specificity of 82%, and a PPV of 76%. A better sensitivity (79%), but lower specificity (76%), was obtained by using two independent thresholds for the two parameters, combined with an "and" operator.

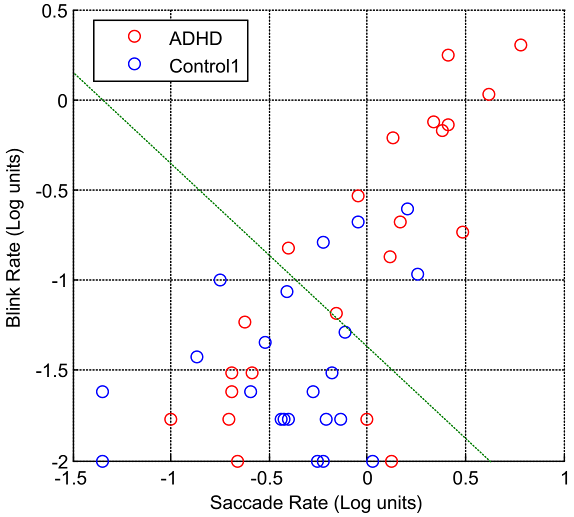

Fig. 12. Differential diagnosis via a linear classification of the microsaccade and blink rates during the peri-stimulus interval. This preliminary attempt yields: accuracy = 70%, sensitivity = 59%, specificity = 82%, and PPV = 76%. Note that both the *x* and *y*-axes are plotted in logarithmic scale.

4. Discussion

In looking for oculomotor markers that could be related to the core deficit in ADHD and that contribute to a more objective and reliable diagnosis, we compared three oculomotor parameters recorded during t.o.v.a. sessions. We compared the averages between the unmedicated ADHD group and a control group, as well as between the unmedicated and the medicated ADHD groups. Our results show that unmedicated ADHD subjects have significantly higher rates of eye blinks and microsaccades, compared with a control group (Figs. 3a and 6a), and that this effect is largest in the peri-stimulus interval (Figs. 3b and 6b) where eye movements should be suppressed because they could interfere with the task. With medication, a striking effect of normalization was found, with full normalization of the microsaccade rate in relation to the control level, and a partial normalization of blink rates, mainly in the peri-stimulus interval (Figs. 3, 6, and 11).

4.1. ADHD and the inhibition of oculomotor activity

We hypothesized that in a task where subjects are required to respond rapidly to visual targets that appear at a regular timing, they will synchronize their transient allocation of attention with the anticipated time of stimulus presentation. This should involve suppression of oculomotor activities, which are known to interfere with the visual input. In particular, we chose to analyze blinks and saccades that involve similar mechanisms (Ridder & Tomlinson, 1997) and are known to prolong reaction times when occurring during stimulus presentation (Johns et al., 2009). Since ADHD subjects are known to be specifically impaired when sustaining their attention in a continuous performance test, as expressed by their typical high rates of false alarms and increased reaction time variability (e.g. (Shalev et al., 2011)), we predicted that they would exhibit lower suppression levels of both blinks and microsaccades

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during the anticipated stimulus presentation. The findings of this study support our prediction. We found a significantly higher average rate of both blinks and microsaccades (8-fold and 3-fold, respectively) in the unmedicated ADHD group, compared with the control groups in the peri-stimulus interval. With medication, these rates were largely reduced, but only the microsaccade rates reached normal levels. We can thus interpret the suppression of microsaccades and blinks around stimulus onset as reflecting a temporal anticipation mechanism for the transient allocation of attention. Our results thus suggest that people with ADHD have a specific impairment in the transient allocation of attention during a continuous performance setting, which could be reduced with medication. In line with this interpretation is a study that found significantly more saccades (>2°) during prolonged fixation in an anti-saccade task in ADHD (Munoz et al., 2003), assuming that microsaccades are just smaller saccades (Martinez-Conde, Otero-Millan, & Macknik, 2013).

Our results regarding blink rate are in line with previous studies, which found blink rates to be negatively correlated with arousal (Tanaka, 1999) and which increase with prolonged wakefulness (Barbato et al., 2007). However, our results are inconsistent with a previous study, which found lower than normal blink rates in unmedicated children with ADHD in a verbal recall task, and higher rates in these children taking medication (Caplan, Guthrie, & Komo, 1996). These opposing results could be attributed to differences in task and modality. In our experiments, subjects had to suppress their eye blinks at the target onset to prevent missing targets or by responding with a delay, and the ADHD subjects often failed to do so.

4.2. ADHD and pupil diameter: light response, transient attention, and arousal

The pupil diameter is known to be affected by three factors that are relevant for the current study: (1) the light response, causing constriction, (2) the transient allocation of attention during which the pupil shows transient dilation (Privitera et al., 2010; Wierda et al., 2012), and (3) the level of arousal, with a larger pupil size reflecting increased arousal (Bradshaw, 1967).

The light response component is particularly strong in the current study due to the very bright stimulus used in the t.o.v.a. paradigm. Although it is impossible to dissociate it from the other components in the current study, its effect can perhaps be appreciated by comparing the pre and post-stimulus intervals (Fig. 11g and h). This comparison yields a more pronounced effect in the ADHD group with and without medication, as expressed by the ratio (pre/post stimulus) plots (Fig. 11i). We intend to further investigate and dissociate this effect in the future by removing it using iso-luminance stimuli in an otherwise similar paradigm, leaving its interpretation for the future.

An estimate of the transient allocation of attention and its efficacy in anticipating the target can perhaps be derived from the pupil diameter and its variability at stimulus onset. We did not find a significant difference in pupil diameter or its variability between groups, but we found a larger pupil diameter (Figs. 9a, 11g and h) and smaller variability (Fig. 9b) with medication. These results are partially inconsistent with our expectation for pupil size expression of a reduced anticipation effect in the ADHD group, as we found for microsaccades and blinks. We noted, however, that such an expectation is based on the assumption that the contribution of transient attention to pupil diameter could be dissociated from the other components, which is clearly not the case in the current data set. On the other hand, the effect of medication is according to our expectation, since it fits the interpretation of enhancing transient attention by medication (a larger pupil at stimulus onset with lower variability). Alternatively, it could be attributed to the effect of medication (MPH) on the balance between constriction and dilation of the pupil at a physiological level (Jaanus, 1992). Finally, the pupil diameter, which is known to be affected by the level of arousal (Bradshaw, 1967), gives us an estimate of arousal, which is of particular importance in discussing the effect of medication (see below).

4.3. ADHD and medication: elevated arousal increases inhibitory oculomotor control

One of the most striking findings of the current study is the normalization effect of medication, i.e. the reduction of microsaccade rates to control levels (Fig. 11a and b). In other words, medication recovers inhibitory oculomotor control of the involuntary eye movements. How is this achieved? One idea is that medication affects a specific mechanism responsible for the transient allocation of attention to anticipated stimuli. These results suggest a different and more general explanation, derived from our results on pupil diameter and microsaccade inhibition at the post-stimulus interval. Since pupil diameter as well as microsaccades are known to be affected by the level of arousal, with a larger pupil (Bradshaw, 1967) and a reduced microsaccades rate (Honda et al., 2013) for higher arousal levels, and since medication consistently dilates the pupil (Fig. 11g and h) and reduces microsaccade rates to control levels (Fig. 11b), we suggest that medication increases inhibitory oculomotor control by elevating the arousal level or the general tonic level of the attention system, consequently increasing the inhibitory power of the system.

4.4. The potential of oculomotor markers for differential diagnosis

In considering the current quantitative oculomotor measures for a differential diagnosis of ADHD, we noted that although the results are highly significant in differentiating between the groups, their diagnostic power at the individual level remains to be further developed and optimized. The classification we obtained (see Section 3) should be regarded as preliminary and is probably lower than the true potential of the findings. For example, the ADHD group was not classified by severity or subtype, and the control group was not screened to exclude ADHD. Therefore, we intend to further investigate these parameters using a more controlled paradigm with diagnosis and medication. Since only the ADHD group was tested with medication, we could not take the observed strong effect of medication as an additional diagnostic parameter, which we believe would add much power to the classification, and this is left for future work.

Our results were obtained in experiments with the t.o.v.a. continuous performance test (CPT), known as a diagnostic tool for ADHD, which is based primarily on response time variability (Greenberg & Waldman, 1993). The t.o.v.a. paradigm was chosen for its simplicity as a continuous performance paradigm that utilizes a fixed inter-stimulus-interval (ISI) during which we could track the regularity and precision of the subjects' oculomotor activities. We also examined another CPT that utilizes variable (random) ISI, the Conjunctive CPT (CCPT) developed by Tsal, Shalev, & Mevorach (Shalev et al., 2011), but this paradigm did not yield a similar difference between the groups. This suggests that the fixed timing is a critical property and that people with ADHD have a specific impairment in the transient allocation of attention for anticipated and regular events. We therefore expect similar results in any continuous performance test with fixed timing.

5. Conclusions

Our study examined the ocular parameters of adults with ADHD, including microsaccade rates, blink rates, and pupil dilation,

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while performing a continuous performance test. Our findings suggest that unmedicated ADHD-diagnosed adults fail to suppress both eye blinks and microsaccades when anticipating a visual target, and that medication improves this anticipatory mechanism. The ocular measures examined in the current study and especially the pattern of microsaccades, are largely involuntary and therefore could potentially serve as an objective physiological marker for diagnosing ADHD.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.visres.2014.05.004.

References

Agay, N., Yechiam, E., Carmel, Z., & Levkovitz, Y. (2010). Non-specific effects of methylphenidate (Ritalin) on cognitive ability and decision-making of ADHD and healthy adults. *Psychopharmacology (Berl), 210*, 511–519.

American Psychiatric Association (2000). *Diagnostic criteria from DSM-IV-TR*. Washington, DC: American Psychiatric Association.

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Arnsten, A. F. T. (2006). Stimulants: Therapeutic actions in ADHD. *Neuropsychopharmacology, 31*, 2376–2383.

Asherson, P., Akehurst, R., Kooij, J. J. S., Huss, M., Beusterien, K., Sasane, R., et al. (2012). Under diagnosis of adult ADHD: Cultural influences and societal burden. *Journal of Attention Disorders, 16*, 20s–38s.

Barbato, G., De Padova, V., Paolillo, A. R., Arpaia, L., Russo, E., & Ficca, G. (2007). Increased spontaneous eye blink rate following prolonged wakefulness. *Physiology & Behavior, 90*, 151–154.

Betta, E., & Turatto, M. (2006). Are you ready? I can tell by looking at your microsaccades. *NeuroReport, 17*, 1001–1004.

Bonneh, Y., Adini, Y., Fried, M., & Arieli, A. (2011). An oculomotor trace of cognitive engagement. *Journal of Vision, 11*, 473.

Bonneh, Y., Adini, Y., Sagi, D., Tsodyks, M., Fried, M., & Arieli, A. (2012). An oculomotor trace of implicit perceptual predictions. *Journal of Vision, 12*, 1114.

Bonneh, Y. S., Donner, T. H., Sagi, D., Fried, M., Cooperman, A., Heeger, D. J., et al. (2010). Motion-induced blindness and microsaccades: Cause and effect. *Journal of Vision, 10*, 22.

Bradshaw, J. (1967). Pupil size as a measure of arousal during information processing. *Nature, 216*, 515–525.

Caplan, R., Guthrie, D., & Komo, S. (1996). Blink rate in children with attention-deficit-hyperactivity disorder. *Biological Psychiatry, 39*, 1032–1038.

Chan, R. C., & Chen, E. Y. (2004). Blink rate does matter: A study of blink rate, sustained attention, and neurological signs in schizophrenia. *The Journal of Nervous and Mental Disease, 192*, 781–783.

Daniels, L. B., Nichols, D. F., Seifert, M. S., & Hock, H. S. (2012). Changes in pupil diameter entrained by cortically initiated changes in attention. *Visual Neuroscience, 29*, 131–142.

de Quiros, G. B., Kinsbourne, M., Palmer, R. L., & Rufo, D. T. (1994). Attention deficit disorder in children: Three clinical variants. *Journal of Developmental and Behavioral Pediatrics, 15*, 311–319.

Gould, T. D., Bastain, T. M., Israel, M. E., Hommer, D. W., & Castellanos, F. X. (2001). Altered performance on an ocular fixation task in attention-deficit/hyperactivity disorder. *Biological Psychiatry, 50*, 633–635.

Greenberg, L. M., & Waldman, I. D. (1993). Developmental normative data on the test of variables of attention (T.O.V.A.). *Journal of Child Psychology and Psychiatry, 34*, 1019–1030.

Guan, L., Wang, B., Chen, Y., Yang, L., Li, J., Qian, Q., et al. (2009). A high-density single-nucleotide polymorphism screen of 23 candidate genes in attention deficit hyperactivity disorder: Suggesting multiple susceptibility genes among Chinese Han population. *Molecular Psychiatry, 14*, 546–554.

Honda, S., Kohama, T., Tanaka, T., & Yoshida, H. (2013). Quantitative evaluation of arousal level based on the analyses of microsaccade rates and pupil fluctuations. *Conference proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Conference, 2013*, 2108–2111.

Jaanus, S. D. (1992). Ocular side effects of selected systemic drugs. *Optometry Clinics, 2*, 73–96.

Johns, M., Crowley, K., Chapman, R., Tucker, A., & Hocking, C. (2009). The effect of blinks and saccadic eye movements on visual reaction times. *Attention, Perception, & Psychophysics, 71*, 783–788.

Kahneman, D., & Beatty, J. (1966). Pupil diameter and load on memory. *Science, 154*, 1583–1585.

Kahneman, D., & Wright, P. (1971). Changes of pupil size and rehearsal strategies in a short-term memory task. *Quarterly Journal of Experimental Psychology, 23*, 187–197.

Kliegl, R., Rolfs, M., Laubrock, J., & Engbert, R. (2009). Microsaccadic modulation of response times in spatial attention tasks. *Psychological Research, 73*, 136–146.

Laubrock, J., Kliegl, R., Rolfs, M., & Engbert, R. (2010). When do microsaccades follow spatial attention? *Attention, Perception, & Psychophysics, 72*, 683–694.

Leark, R. A., Wallace, D. R., & Fitzgerald, R. (2004). Test-retest reliability and standard error of measurement for the test of variables of attention (T.O.V.A.) with healthy school-age children. *Assessment, 11*, 285–289.

Martin, L., Aring, E., Landgren, M., Hellstrom, A., & Andersson Gronlund, M. (2008). Visual fields in children with attention-deficit/hyperactivity disorder before and after treatment with stimulants. *Acta Ophthalmologica, 86*, 259–264.

Martinez-Conde, S., Otero-Millan, J., & Macknik, S. L. (2013). The impact of microsaccades on vision: Towards a unified theory of saccadic function. *Nature Reviews Neuroscience, 14*, 83–96.

McBurnett, K., & Starr, H. L. (2011). OROS methylphenidate hydrochloride for adult patients with attention deficit/hyperactivity disorder. *Expert Opinion on Pharmacotherapy, 12*, 315–324.

McCamy, M. B., Otero-Millan, J., Macknik, S. L., Yang, Y., Troncoso, X. G., Baer, S. M., et al. (2012). Microsaccadic efficacy and contribution to foveal and peripheral vision. *Journal of Neuroscience, 32*, 9194–9204.

Munoz, D. P., Armstrong, I. T., Hampton, K. A., & Moore, K. D. (2003). Altered control of visual fixation and saccadic eye movements in attention-deficit hyperactivity disorder. *Journal of Neurophysiology, 90*, 503–514.

Nagyova, K., Szabo, K., Vetro, A., & Tokaji, Z. (2007). Methylphenidate-induced stabilization of the sympathetic/parasympathetic tone in children with ADHD. *European Neuropsychopharmacology, 17*, S574–S575.

Pastukhov, A., & Braun, J. (2010). Rare but precious: Microsaccades are highly informative about attentional allocation. *Vision Research, 50*, 1173–1184.

Pastukhov, A., Vonau, V., Stonkute, S., & Braun, J. (2012) Spatial and temporal attention revealed by microsaccades. *Vision Research*.

Poltavski, D. V., Biberdorf, D., & Petros, T. V. (2012). Accommodative response and cortical activity during sustained attention. *Vision Research, 63*, 1–8.

Privitera, C. M., Renninger, L. W., Carney, T., Klein, S., & Aguilar, M. (2010). Pupil dilation during visual target detection. *Journal of Vision, 10*, 3.

Ridder, W. H., 3rd, & Tomlinson, A. (1997). A comparison of saccadic and blink suppression in normal observers. *Vision Research, 37*, 3171–3179.

Rolfs, M. (2009). Microsaccades: Small steps on a long way. *Vision Research, 49*, 2415–2441.

Shalev, L., Ben-Simon, A., Mevorach, C., Cohen, Y., & Tsal, Y. (2011). Conjunctive continuous performance task (CCPT) – A pure measure of sustained attention. *Neuropsychologia, 49*, 2584–2591.

Simpson, H. M. (1968). Effects of a task relevant response on pupil size. *Canadian Psychologist – Psychologie Canadienne, 9*, 291–300.

Tanaka, Y. (1999). Arousal level and blink activity. *Shinrigaku kenkyu: The Japanese Journal of Psychology, 70*, 1–8.

Valsecchi, M., Betta, E., & Turatto, M. (2007). Visual oddballs induce prolonged microsaccadic inhibition. *Experimental Brain Research, 177*, 196–208.

Wender, P. H., Wolf, L. E., & Wasserstein, J. (2001). Adults with ADHD. An overview. *Annals of the New York Academy of Sciences, 931*, 1–16.

Wierda, S. M., van Rijn, H., Taatgen, N. A., & Martens, S. (2012). Pupil dilation deconvolution reveals the dynamics of attention at high temporal resolution. *Proceedings of the National Academy of Sciences of United States of America, 109*, 8456–8460.

Zelnik, N., Bennett-Back, O., Miari, W., Goez, H. R., & Fattal-Valevski, A. (2012). Is the test of variables of attention reliable for the diagnosis of attention-deficit hyperactivity disorder (ADHD)? *Journal of Child Neurology, 27*, 703–707.

Please cite this article in press as: Fried, M., et al. ADHD subjects fail to suppress eye blinks and microsaccades while anticipating visual stimuli but recover with medication. *Vision Research* (2014), http://dx.doi.org/10.1016/j.visres.2014.05.004